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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,837	09/04/2001	Kenya Shitara	249-188	4386

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 12/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)	
Office Action Summary	09/914,837	SHITARA ET AL.	
	Examiner	**Art Unit**	
	Christopher H. Yaen	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,24,26,27 and 29-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24,26,27 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Shitara *et al*

1. The amendment filed 9/6/2005 is acknowledged and entered into the record. Accordingly, claims 1-21,23, 25, and 28 are canceled without prejudice or disclaimer, and claim 32 is newly added.

2. Claims 22,24,26-27,29-32 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Upon further review and reconsideration, the species election made on 10/02/2003 is hereby withdrawn.

Claim Rejections Maintained - 35 USC § 103

5. The rejection of claims 22,24,26-27,29-31 and now newly added claim 32 under 35 USC § 103 as being obvious over Bellamy *et al* in view of Shitara *et al*, Rockwell *et al* and now newly cited Greenwood *et al* ("Effector functions of matched sets of recombinant human IgG subclass antibodies *"Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man"* Alden Press/Academic Titles 1993; pages 85-100) is maintained for the reasons of record. Applicant argues that the cited references do not teach nor suggest a method of treating leukemia using a humanized antibodies against the VEGF flt-1 receptor, wherein the antibody exhibits ADCC activity. Specifically, applicant indicates that Shitara *et al* (US Patent 6,617,160) is *"understood to disclose neutralizing antibodies against Flt-1, while*

neither disclosing nor suggesting a humanized anti-flt-1 antibody having ADCC activity."

Applicant further contends that the antibodies taught by the cited prior art (i.e. Shitara *et al* and Rockwell *et al*) only disclose antibodies capable of inhibiting signal transduction and does not teach antibodies that "injury" leukemic cells. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

One of ordinary skill in the art would find the instant invention obvious in view of the combination of cited references of Bellamy *et al* in view of Shitara *et al* and Rockwell *et al*. Specifically, at the time the invention was made, Bellamy *et al* taught that hematopoietic cells, such as leukemic cells, expressed the Flt-1 receptor. Shitara *et al* taught the specific flt-1 receptor antibodies and further disclosed specific species of flt-1 receptor antibodies (i.e. KM-1730, KM-1731, KM-1732, KM-1748, and KM-1750). Moreover, Shitara *et al* characterized the isotypes of the said antibodies as being in IgG1 (i.e. KM-1730 and KM-1732), IgG2a (i.e. KM-1731), or IgG2b (i.e. KM-1748 and KM-1750) subclasses (see col. 4). Although neither Bellamy *et al* nor Shitara *et al* taught humanized forms of the flt-1 antibodies, Rockwell *et al* taught that at the time the invention was made, humanization of antibodies against the VEGF flt-1 receptor was well known and practiced and was capable of treating Flt-1 related diseases (see claims 23-27, in particular). Thus the combination of the references taught the instant invention as a whole.

Although Shitara *et al* does not specifically indicate that the KM-1732 antibody was capable of eliciting ADCC activity, the specification of the instant invention has

defined the IgG1 and IgG2a in mice and IgG1 in humans as having ADCC activity (see in particular page 29 of the specification). Moreover, Greenwood *et al* teaches that antibodies of the IgG1 subclass are well known to have ADCC activities (see figure 1, in particular). One of skill in the art would therefore find it obvious that the different antibodies as disclosed by Shitara *et al* would be capable of functioning via ADCC activity as claimed. Thus, the amendment to the claims would have been obvious to one of ordinary skill in the art at the time the invention was made.

Applicant further contends that Bellamy *et al* discloses leukemic cells expressing bFGF in addition to VEGF and that IL-6 is an important factor for proliferation of leukemia. Applicant concludes the antibodies as taught by Shitara *et al* and Rockwell *et al* cannot inhibit signaling from other signaling transduction factors such as bFGF or IL-6 and thus one of skill in the art would not have been able to recognize or make obvious the instant invention. Applicant's arguments have been carefully considered, but are not deemed persuasive to overcome the rejection of record. The claims of the instant invention *comprise* the administration of a humanized anti-human VEGF receptor flt-1 antibody. The claims are written in open language and therefore does not preclude the administration of other antibodies or compounds that inhibit the signals mediated by bFGF or IL-6.

Therefore the rejection of claims under 35 USC 103(a) as being obvious is maintained for the reasons of record.

New Arguments

Claim Rejections - 35 USC § 112, 1st paragraph

6. Claims 22,24,26-27, and 29-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION. Claim 22 and its dependent claims have been newly amended to recite "antibody-dependent cellular cytotoxic activity against leukemic cells." Applicant has not pointed to specific support in the specification as filed. Moreover, the specification as filed does not specifically support a method of treating leukemia by the means of antibody-dependent cellular cytotoxic or ADCC. The specification on page 29 teaches that the IgG1 subclass display both complement-dependent cytotoxicity and ADCC, however nowhere in the specification does it specifically disclose the mechanism of ADCC for the treatment of leukemia as claimed.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 24 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 24 and 32 recite specific clones of antibodies. It is apparent that the recited antibodies are required to practice the claimed invention, because they are

specifically required in the claims. As required elements they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the antibody or hybridoma cell line producing said antibodies. See 37 CFR 1.802.

The specification on page 27-28 discloses hybridoma cell lines which produce the specific antibody clones, however no information is provided regarding the public availability of claimed antibody nor is there any information provided regarding a repeatable method for obtaining the claimed antibodies or the hybridoma cell lines disclosed. Deposit of the cell lines would satisfy the enablement requirements of 35 U.S.C. 1121st paragraph.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or

her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements. Applicant is reminded that the terms of the deposit must be clearly stated.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1643
November 21, 2005

CHRISTOPHER YAEN
PATENT EXAMINER